# Kinetic Studies of the Azo Coupling Reaction between 1-(4-Hydroxy-6-methylpyrimidin-2-yl)-3-methylpyrazolin-5-one and Substituted Benzenediazonium Salts

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Kinetic studies have been carried out on the azo coupling reactions between 1-(4-hydroxy-6-methylpyrimidin-2-yl)-3-methylpyrazolin-5-one and seven substituted benzenediazonium salts. The effects of acidity and temperature upon the rate have been investigated and activation parameters determined, and the involvement of deprotonated substrate in the rate determining step demonstrated. Acid dissociation equilibrium of the substrate is characterized by $pK_a^{HA} = 5.07 \pm 0.16$ at 293 K and $\mu = 0.2$. Close activation enthalpies, between 48 and 59 kJ mol^{-1} and negative entropies between -22 and -53 J mol^{-1} K^{-1} have been found, depending on the electronic effects of substituents on the benzene nucleus of the diazonium salts. A Hammett relationship $\log_{10} k_2 = 1.0 \pm 0.1 + (3.3 \pm 0.3)\sigma$ holds for coupling reactions. The greater the electron-withdrawing effect, the faster is the coupling rate. 1-(2-Pyrimidinyl)pyrazolin-5-one behaves similarly to 1-arylpyrazolin-5-one and phenols in reactions with arenediazonium cations.

The employment of coupling reactions between 1-phenyl-3-methylpyrazolin-5-one (**1**) and benzenediazonium salts (**2**) to yield a series of commercial dyestuffs (**3**)[1-3] has stimulated kinetic investigations of these processes. Kinetic studies[4-6] have revealed an analogy between the mechanisms of coupling reactions of 1-arylpyrazolin-5-one (**1**) and those of phenols. The active form of the coupling component has been considered to be an anion for both reactions, as illustrated by Scheme 1.[6]

1; X = CH₃

2   **4**

3
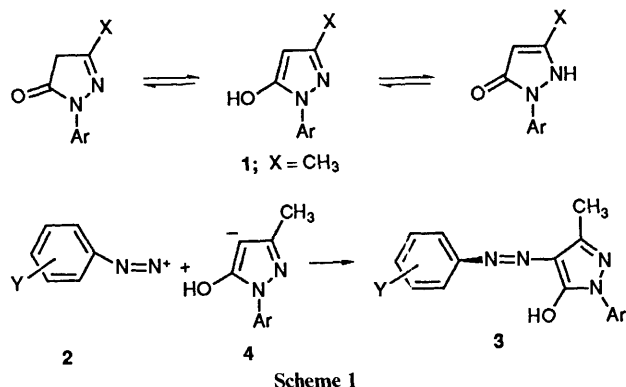
Scheme 1

A series of 1-(2-pyrimidinyl)-3-methylpyrazolin-5-ones (**5**) were recently synthesized[7-9] and, by coupling with substituted benzenediazonium salts (**2**), yielded a large number of new azo dyestuffs[10] (Scheme 2). The reaction rate of 1-(2-pyrimidinyl)-3-methylpyrazolin-5-one (**5**) and diazonium salts increased with the pH of the solution, suggesting the involvement of an anion, similar to the reaction of 1-phenyl-3-methylpyrazolin-5-one (**1**) (see **4**).[4-6]

The purpose of this paper is a kinetic study under various experimental conditions of the coupling reaction between the title pyrimidinylpyrazolone **7** (**5** with R = H; Z = OH) and substituted benzenediazonium salts (**2**), and a comparison with 1-phenyl-3-methylpyrazolin-5-one (**1**), which has been previously studied in the literature.[4-6] It is worth mentioning that aspects concerning the tautomerism of 1-arylpyrazolin-5-one as well as of the corresponding azo dyes (**3**) are discussed in the literature.[4-6,11-13] Therefore, we will use only one tautomeric form, like **5** or **6**, keeping in mind the possibility of involvement of the others.

2

5

6
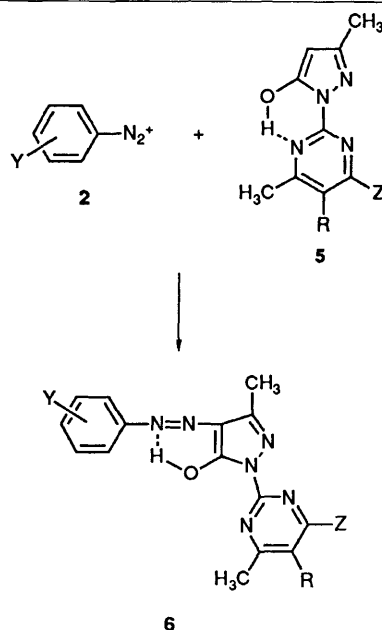
Scheme 2 Y = H; alkyl; halogen; CH_3O-; HOOC-; HO_3S-; O_2N-; $(CH_3)_2N$-. R = H; alkyl (C_1-C_4). Z = HO-; Cl-; CH_3O-; C_2H_5O-.
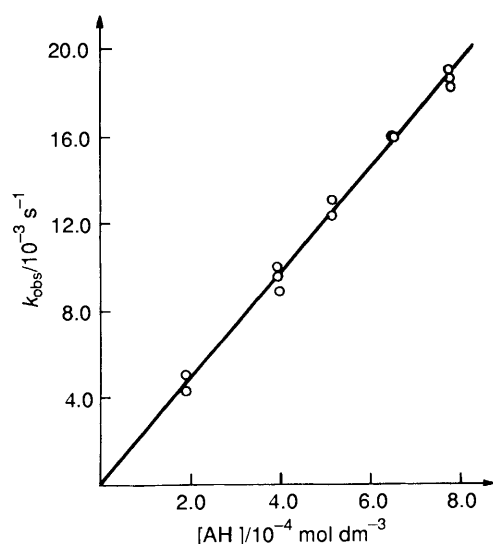
Experimental

The amines were either commercial products or were prepared by standard methods. Benzenediazonium salt solution was prepared by dissolving a known amount of amine in a small volume of 2.5 mol dm^{-3} HCl solution, cooling it in an ice bath and addition, in portions, of 1.1 equivalents of $NaNO_2$ solution. The excess of nitrous acid was removed by addition of sulfamic acid. The solution was made up to the mark in a volumetric flask and aliquots diluted to concentrations used in the kinetic runs. Stock solution was freshly prepared before each set of runs, kept in the refrigerator, and not used more than 5 h after preparation, to avoid hydrolytic decomposition. 1-(4-Hydroxy-6-methyl-pyrimidin-2-yl)-3-methylpyrazolin-5-one (**7**) was prepared as previously described[7,8] and purified by recrystallisation from ethanol. The purity was checked by thin-layer chromatography.

A stock solution was obtained by weighing a known amount

Table 1 Observed first-order rate constant k_{obs} and stoichiometric rate constant k_s at 293 K, pH = 5.00 and μ = 0.2

Y	λ_{max}/nm	[7]/10^{-4} mol dm^{-3}	[Y-$C_6H_4N_2^+$]/10^{-5} mol dm^{-3}	k_{obs}/10^{-3} s^{-1}	k_s/dm^3 mol^{-1} s^{-1}
p-CH$_3$O	430	4.62	1.95	0.26	0.56
p-CH$_3$	450		2.33	0.45	0.98
H	420		2.02	2.66	5.76
p-Cl	430		2.24	13.4	29.2
p-Br	425	2.31	1.96	6.37	27.6
		4.62	2.00	13.2	28.6
p-HO$_2$C	435		2.02	17.8	38.5
p-HO$_3$S	420		2.00	28.5	61.7
p-O$_2$N	420		2.20	too fast to be measured	

Fig. 1 Dependence of observed first-order rate constants on pyrimidinylpyrazolone (7) concentration at 294 K, pH = 5.20, [$C_6H_5N_2^+$] = 3.15 × 10^{-5} mol dm^{-3} and μ = 0.17

of **7**, dissolving it in hot water and diluting to the concentration needed in the kinetic run with acetate buffer. All solutions were made up using distilled water.

The dissociation constant of **7** was measured at 20 °C and ionic strength 0.2 by the method of potentiometric titration.[14] Aliquots of 0.1–0.2 cm^3 of 0.1 mol dm^{-3} KOH solution were gradually added to 100 cm^3 of a 2 × 10^{-3} mol dm^{-3} solution of **7** and pH values were measured by means of a digital pH-meter. Volume corrections have been taken into account in the computation of K_a^{HA}.

Kinetic measurements were performed spectrophotometrically at an appropriate wavelength, following the formation of dyestuff. A Zeiss Spekol spectrophotometer was used.

Reactions were started by injection of 0.4 cm^3 of a 0.1 mol dm^{-3} diazonium salt solution, thermostatted at the temperature of reaction, to 1.6 cm^3 of a solution of **7** in a 1 cm path length cell. A plastic syringe of 0.5 cm^3 was used to mix reacting solutions, mixing time was not longer than 0.3 s. A large excess of **7** was used to ensure pseudo-first-order conditions.

The increase of absorbance was monitored until a constant value was reached, corresponding to the final concentration of dyestuff which could be obtained under the experimental conditions used (*ca.* 2 × 10^{-5} mol dm^{-3}). The final readings corresponded to those measured with solutions of pure dyestuff into which an identical excess of **7** was added. This proved that the diazonium salt did not decompose significantly during the kinetic run.

Ionic strength was adjusted by addition of 1.0 mol dm^{-3} KCl to each solution before mixing. The experimental pH values were obtained with acetate–acetic acid buffers, and were measured at the end of the kinetic run. The cell temperature was

maintained by circulation of water from a thermostat, controlled to within ±0.05 °C, through the temperature jacket of the cellholder.

Results and Discussion

The amines used to prepare diazonium salts are listed in Table 1 along with the wavelength at which the dyestuff formation was followed. p-O_2N–$C_6H_4N_2$Cl reacted too fast to be measured by the technique used here.

Under the conditions of a large excess of pyrimidinyl-pyrazolone **7**, all coupling reactions followed first-order kinetics. The absorbance data obtained fulfilled the linear relation of eqn. (1) to more than 90% completion at low

$$\ln(A_\infty - A) = \ln(A_\infty - A_0) - k_{obs}t \qquad (1)$$

temperatures and acidic pH, and to 75–80% completion at temperatures exceeding 298 K and neutral pH. The subscripts '0' and '∞' indicate the readings at initial and final points respectively. When identical reagent solutions were used under the same conditions, reproducibility between runs was good (within 2–4%). Because scatter increased with increasing conversion at relatively low diazonium salt concentration (*ca.* 10^{-5} mol dm^{-3}), two to four individual runs, performed under the same conditions, were considered to obtain the pseudo-first-order rate constant. A least-squares procedure was used and correlation coefficients ranged between 0.991 and 0.999.

In order to ascertain the dependence of the observed rate coefficients on pyrimidinylpyrazolone (**7**) concentration, we performed kinetic measurements at a constant initial concentration of benzenediazonium cation and various excess concentrations of **7**. Fig. 1 shows this dependence. It can be seen that, within experimental error, observed first-order rate constants were proportional to the excess concentration of **7**, proving a first-order relationship with respect to **7** as well. Stoichiometric second-order rate constants k_s could be obtained from the slopes of lines [eqn. (1)] divided by the concentration of **7**. The last column of Table 1 contains values of k_s at 293 K and μ = 0.2.

Conclusions regarding the nature of the active species involved in the coupling reaction with diazonium cation can be obtained from the influence of hydrogen ion concentration on the rate.[4–6] Therefore, reactions with $C_6H_5N_2^+$, p-CH$_3$O–$C_6H_4N_2^+$ and p-Cl-$C_6H_4N_2^+$, were carried out at different hydrogen ion concentrations within the pH range 4.00–7.80. Measurements were not possible at higher pH because hydrolytic decomposition of diazonium cation occurred very rapidly, and a subsequent coupling reaction with phenol took place as well. A plot of log k_s *versus* pH (Fig. 2) shows a linear dependence at acidic pH, with a curvature and a trend to a limiting value towards neutral or alkaline pH. This behaviour indicates the involvement of an anion of pyrimidinylpyrazolone (**7**) in the rate determining step of the coupling process [eqn. (2)]

$$Y\text{-}C_6H_4\text{-}N_2^+ + A^- \xrightarrow{k_2} Y\text{-}C_6H_4\text{-}N_2\text{-}A \qquad (2)$$
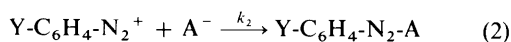
rather than the neutral **7** molecule and the rate law is given by eqn. (3) where A^- stands for acid dissociated pyrimidinylpyra-

$$\text{rate} = k_2[Y\text{-}C_6H_4\text{-}N_2^+][A^-] \qquad (3)$$

zolone (**7**). To determine the true second-order rate coefficient k_2, the acid dissociation constant K_a^{HA} for **7** was required. The coupling agent **7** has been considered as a monobasic acid, similar to other phenylpyrazolones.[4-6] Using a titration method[14] and taking into account the concentration balances for **7** and hydroxide ion, the dissociation equilibrium constant has been calculated from eqn. (4) where $[HA]_t$ stands for

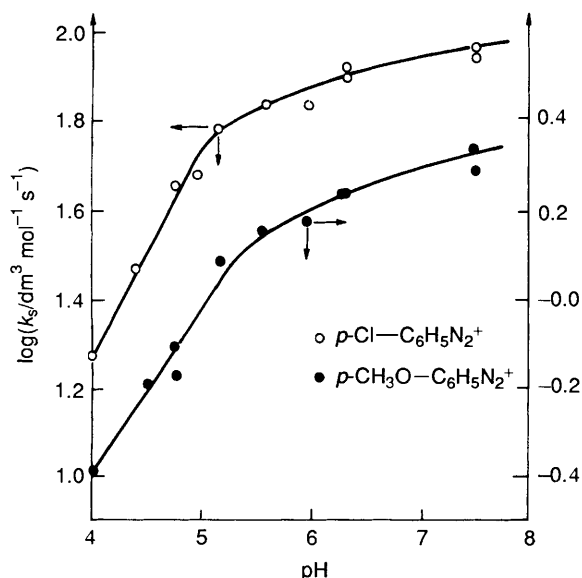$$K_a^{HA} = \frac{[H^+]\{[OH^-]_{add} - K_w/[H^+]\}}{[HA]_t - [OH^-]_{add} + K_w/[H^+]} \qquad (4)$$

Fig. 2 Plot of $\log_{10}k_s$ *versus* pH at 294 K and $\mu = 0.17$

Table 2 Data for the acid dissociation constant K_a^{HA} of pyrimidinyl-pyrazolone (**7**) at 293 K and $\mu = 0.2$

Vol. KOH (0.1 mol dm⁻³) added/cm³	pH	pK_a^{HA}
0.2	4.34	5.27
0.4	4.52	5.09
0.5	4.62	5.08
0.6	4.73	5.06
0.7	4.83	5.06
0.8	4.96	5.09
1.0	5.12	5.05
1.1	5.20	5.03
1.3	5.37	5.02
1.4	5.46	5.00
		Mean: 5.1 ± 0.2

analytical concentration of **7**, $[OH^-]_{add}$ analytical concentration of KOH after each volume addition to the solution and K_w ionization constant for water. Data are contained in Table 2. A mean value of $pK_a^{HA} = 5.07 \pm 0.16$ was obtained at 293 K and $\mu = 0.2$ (standard deviation 0.07). Another experiment at 293 K and $\mu = 0.14$ gave $pK_a^{HA} = 5.35 \pm 0.18$. The acidities of active methylene (or other tautomeric form) in substituted pyrazolones are presented in Table 3. Values of pK_a^{HA} depend on the nature of substituents in the 1 and 3 positions. The pyrimidinyl ring brings about an increase in acidity as compared to the phenyl ring. By means of K_a^{HA}, the true bimolecular rate coefficient k_2 can be calculated according to eqn. (5). Table 4 contains values of k_2 calculated with eqn. (5) at

$$k_2 = k_{obs} \frac{K_a^{HA} + [H^+]}{K_a^{HA}[HA]_t} = k_s \frac{K_a^{HA} + [H^+]}{K_a^{HA}} \qquad (5)$$

different hydrogen ion concentration for the reaction of **7** with $C_6H_5N_2^+$, and at constant pH = 5.00 for the reactions with the other diazonium cations. For various pH values, second-order rate coefficients k_2 obtained were in good agreement. A mean of 13.00 ± 0.50 dm³ mol⁻¹ s⁻¹ (standard deviation: 0.24) was obtained. This agreement in k_2 values provides support for the involvement of pyrimidinylpyrazolone anion (like **4**) in the transition state formation. The coupling reaction with neutral substituted pyrazolone, if it occurs at all, is much slower, by several orders of magnitude, than reaction with its anion.[4-6]

The effects of substituents on the benzene nucleus of diazonium salts upon the rate could be assessed by a Hammett relationship, which holds for a series of coupling reactions.[4,15,16] Substituent constants σ used[17] are given in Table 4. The dependence of k_2 on Hammett constant σ is expressed by eqn. (6). A good linearity was obtained (Fig. 3).

$$\log_{10}k_2 = (1.0 \pm 0.1) + (3.3 \pm 0.3)\sigma \qquad (6)$$

Standard deviation of the slope was 0.162 and a correlation coefficient of 0.993 was found.
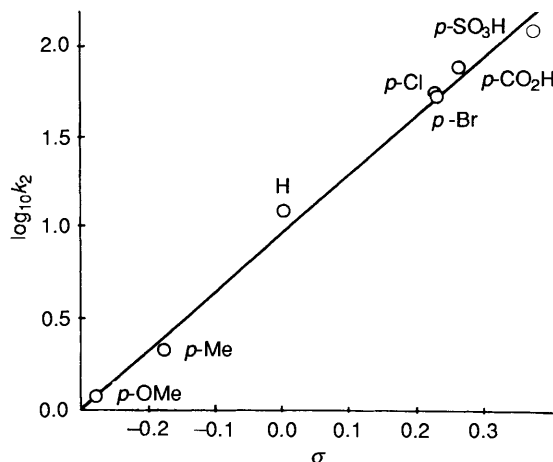

Fig. 3 Hammett plot of $\log_{10}k_2$ *versus* substituent constant σ

Table 3 Values of pK_a^{HA} for several substituted pyrazolones at 293 K and $\mu = 0.2$–0.25, and k_2 for coupling reactions with $HO_3S\text{-}C_6H_4\text{-}N_2^+$

Compound	X	Ar	pK_a^{HA}	k_2/dm³ mol⁻¹ s⁻¹	Reference
1	NH_2	C_6H_5	9.30	6.94×10^5	6
	CH_3	C_6H_5	7.15	6.65×10^4	4
	$CO_2C_2H_5$	C_6H_5	4.49	1.37×10^2	5
	CH_3	$HO_3SC_6H_4$	6.65	1.92×10^4	4
7			5.07	1.35×10^2	This work

The kinetic results are consistent with a bimolecular electrophilic substitution as far as sign and value of the ρ constant is concerned.[4,6] Electron-withdrawing substituents on the benzene ring of the diazonium cation enhance the rate, while electron-releasing substituents reduce it.[18]

Table 4 Second-order rate constant k_2 at 293 K and $\mu = 0.2$

Y	σ	pH	k_2/dm³ mol⁻¹ s⁻¹
H	0.0	4.23	13.1
		4.67	13.2
		5.00	12.6
		5.37	13.0
		6.12	12.7
		6.37	13.1
			Mean: 13.0 ± 0.5
p-CH₃O	−0.27	5.00	1.2
p-CH₃	−0.17	5.00	2.1
p-Cl	0.23	5.00	63.7
p-Br	0.23	5.00	60.2
			62.4
p-HO₂C	0.26	5.00	84.2
p-⁻O₃S	0.38	5.00	135.0

The similar behaviour of 1-(2-pyrimidinyl)pyrazolin-5-ones (**5**) and 1-phenylpyrazolin-5-one (**1**) in azo coupling reactions is clearly revealed by comparison of the k_2 values obtained in the reaction with the diazonium salt from sulfanilic acid (see Table 3). We have found $k_2 = 1.35 \times 10^2$ dm³ mol⁻¹ s⁻¹ for **7**, while 1-phenyl-3-ethoxycarbonylpyrazolin-5-one has given $k_2 = 1.37 \times 10^2$ dm³ mol⁻¹ s⁻¹ at 293 K. The values of pK_a^{HA} for the two substrates are very close. Close values of specific velocity k_2, determined from close values of pK_a^{HA} are expected, because linear correlations of k_2 with K_a^{HA} have been described in the literature[5,6] for azo coupling reactions of various substrates with the same diazonium cation.

Interaction between two species with opposite charges should require a relatively low activation barrier. The temperature dependence of the rate has been studied in the range 280–307 K at constant pH = 5.00. Table 5 collects the kinetic data necessary to obtain the experimental activation energy, activation enthalpy and entropy. A least-squares procedure has been used for determination of E_a, $\Delta H^\ddagger$, and a good linearity was observed (correlation coefficients between 0.992 and 0.998). Activation enthalpies are relatively close together for all the systems investigated, within the range 48–59 kJ mol⁻¹. Their values are quite low, as expected for the

Table 5 The effect of temperature on the rate of the coupling reaction between **7** and diazonium salts at pH = 5.00 and $\mu = 0.2$

Salt	T/K	k_{obs}/10⁻⁴ s⁻¹	k_s/dm³ mol⁻¹ s⁻¹	E_A/kJ mol⁻¹	$\Delta H^\ddagger$/kJ mol⁻¹	$\Delta S^\ddagger$/J mol⁻¹ K⁻¹
CH₃O-C₆H₄N₂⁺	281	1.01	0.22	60 ± 1	58 ± 1	−44 ± 4
	283	1.12	0.24			
	286	1.50	0.33			
	288	1.55	0.34			
	293	2.61	0.56			
	300	5.17	1.12			
CH₃-C₆H₄N₂⁺	281	1.53	0.33	59 ± 1	56 ± 1	−47 ± 4
	283	1.68	0.36			
	286	2.32	0.50			
	293	4.51	0.98			
	296	5.46	1.18			
	307	12.3	2.65			
C₆H₅N₂⁺	281	9.6	2.08	52.3 ± 0.5	49.9 ± 0.6	−54 ± 2
	283	11.5	2.48			
	288	16.9	3.65			
	293	26.6	5.76			
	300	41.3	8.93			
	303	47.3	10.2			
Cl-C₆H₄N₂⁺	281	57	12.3	53.1 ± 0.7	51 ± 1	−44 ± 3
	283	62	13.3			
	286	75	16.2			
	291	106	23.0			
	293	135	29.2			
	295	146	31.6			
	296	181	39.1			
	303	282	61.0			
Br-C₆H₄N₂⁺	280	22	9.7	56.0 ± 0.8	54 ± 1	−29 ± 4
	283	27	11.6			
	286	35	15.2			
	290	48	20.9			
	293	64	27.6			
	298	93	40.2			
	303	131	56.5			
HO₂C-C₆H₄N₂⁺	280	58	12.6	58 ± 1	53 ± 1	−21 ± 4
	283	80	17.2			
	288	112	24.1			
	293	178	38.5			
	298	265	57.4			
HO₃S-C₆H₄N₂⁺	281	110	23.8	51 ± 1	48 ± 2	−39 ± 5
	283	131	28.4			
	288	194	42.0			
	291.5	236	51.1			
	293	285	61.7			
	297	352	76.2			

formation of a transition state by association of two oppositely charged ions.

The activation entropy was derived from true second-order rate coefficient k_2 at 293 K and $\Delta H^{\ddagger}$ obtained from the slope of the line $\ln(k_s/T)$ as a function of $1/T$, because K_a^{HA} was measured only at 293 K. Precision of $\Delta S^{\ddagger}$ was calculated following the method of Petersen et al.,[19] taking into account precision of $\Delta H^{\ddagger}$ and that of k_2. Activation entropies obtained in such a way were negative and not very large. Except for reaction with p-SO$_3$H- substituted benzenediazonium salt, in which the sulfonic group is dissociated at pH = 5.00, it seems likely that a correlation between activation entropy and electronic effects of substituents on the diazonium cation exists. Although only an unsatisfactory linear relationship has been observed [$\Delta S^{\ddagger} = -41 \pm 5 + (33 \pm 21)\sigma$; correlation coefficient 0.62], because activation enthalpies were not the same for all reacting systems, it seems that the larger the electron-withdrawing effect (the more positive the substituent constant σ), the less negative the activation entropy. Electron-releasing substituents bring about a large dispersion of positive charge on the diazonium cation, while electron-withdrawing substituents, induce a very localized charge at the side chain, involved in bond formation during the reaction. When the transition state has been formed, opposite dispersed charges on anion and cation are not completely neutralized. Solvation of the transition state is determined by the degree of charge neutralization. With electron-releasing substituents on the diazonium cation, the solvation is less diminished compared to separate ions, and the entropy change is very negative. With electron-withdrawing substituents, in contrast, solvation of the transition state is much diminished as compared to the ground state of reactants (charges neutralized to a larger degree), and the entropy change is less negative.

The results and considerations presented above support the following mechanism operating in these azo coupling reactions: a fast base-catalysed deprotonation pre-equilibrium of pyrimidinylpyrazolone (7), followed by the rate-determining electrophilic attack of diazonium cation upon the pyrimidinylpyrazolone anion. Further study is in progress in our laboratory, and some other systems will be investigated, to search for the effect of substituents on pyrazolone and pyrimidinyl rings upon the reaction velocity.

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